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Growth Hormone Deficiency (GHD): Assessing Burden of Disease in Children and Adolescents: the Growth Hormone Deficiency – Child Impact Measure (GHD-CIM)

Meryl Brod;[1] Michael Højby Rasmussen;[2] Knud Vad;[2] Suzanne Alolga;[1] Jacques Bedoin[2]

[1]The Brod Group, Mill Valley, CA 94941 USA; [2]Novo Nordisk A/S, Global Development, Søborg, Denmark

Introduction

- Children with growth hormone deficiency (GHD) may have to deal with practical, emotional, and functional difficulties. To date, there is no condition-specific measure of the impact of GHD for these children.
- The Growth Hormone Deficiency – Child Impact Measure (GHD-CIM) was developed according to United States (US) Food and Drug Administration/European Medicine Agency guidelines to address this gap.[1,2]
- Psychometric testing was conducted for the GHD-CIM to determine measurement properties, reliability, validity, and interpretability of the measure.
  - The preliminary GHD-CIM had two versions: a child self-report (PRO) for ages 9 to less than 13 years and an observer-report (ObsRO) for parents/guardians of children aged 4 to less than 9 years.
  - However, preliminary analysis raised concerns about floor and ceiling effects; therefore, the preliminary 20-item version (validation data shown in abstract) was further refined to an 11-item version which reduced these effects.
- This study presents the psychometric validation results of the refined GHD-CIM 11-item version.

Methods

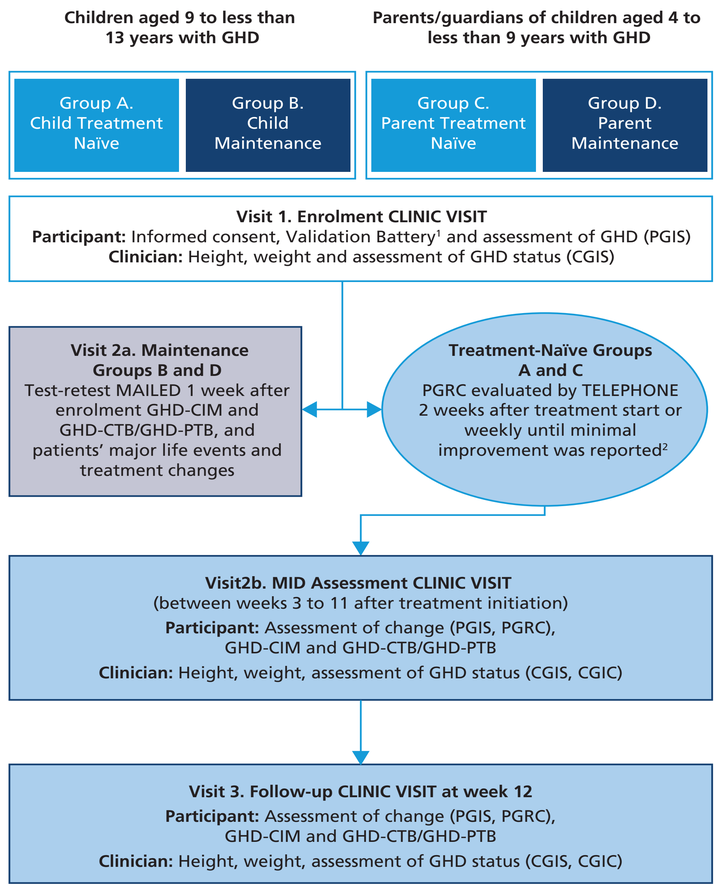
Study design

- A non-interventional, multi-clinic-based validation study was conducted in the USA and the United Kingdom.
- Two populations of participants were recruited:
  - Pre-pubertal children aged 9 to less than 13 years with a diagnosis of GHD and parents/guardians of younger children with GHD aged 4 to less than 9 years.
  - Each population was further divided into a Treatment-Naïve group (Group A or Group C) or Maintenance group (Group B or Group D) for a total of four subgroups and no control group (**Figure 1**).
- All groups completed a baseline assessment battery in clinic, with in-person follow-up for the Treatment-Naïve groups (**Figure 1**).
- Patients were treated with commercially available products according to routine clinical practice at the discretion of their treating physician.

Statistical analysis plan

- Exploratory factor analysis procedures on the correlation matrices derived from the items comprising the GHD-CIM measures and confirmatory factor analysis to verify the final factor structure derived were performed.
- Items were considered for deletion for reasons of high correlation with other items or total score, floor or ceiling effects, poor fit or conceptual relevance considerations.
- Cronbach's alpha was used to assess internal consistency reliability. A minimum correlation of 0.70 was expected.
- Test-retest reliability was assessed using the intraclass correlation coefficient (ICC) in a subsample from the Maintenance groups who indicated experiencing no change in treatment since their last assessment.
- Convergent construct validity was assessed with Pearson's correlation between measure scores and other items or instruments measuring similar concepts, and supported when the scores were substantially correlated (≥0.40).
- Known-groups validity was also tested for hypotheses using a two-tailed test at a $p<0.05$ level and was supported when at minimum one hypothesis per subdomain was significant.

Figure 1 ♦ Overview of study design



1. The GHD-CIM and GHD-CTB/GHD-PTB were completed by the Maintenance Group at the enrolment clinic visit. For the Treatment-Naïve Group, the GHD-CIM was completed at the enrolment visit, and the GHD-CTB/GHD-PTB was taken home to complete 1 week after treatment start and then returned by mail.
2. Telephone assessment of improvement was conducted weekly until minimal improvement was reported. Once reported, their MID assessment clinic visit was scheduled to occur within one week.

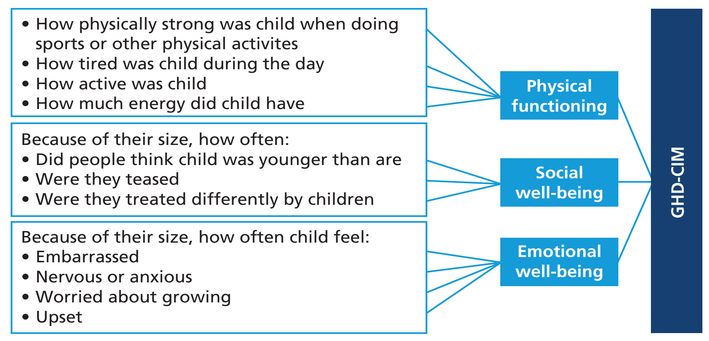
GHD-CIM, Growth Hormone Deficiency – Child Impact Measure; GHD-CTB, Growth Hormone Deficiency – Child Treatment Burden Measure; GHD-PTB, Growth Hormone Deficiency – Parent Treatment Burden Measure; PGIS, Patient Global Impression of Severity; PGRC, Patient Global Rating of Change; CGIS, Clinician Global Impression of Severity; CGIC, Clinician Global Impression of Change; MID, Minimally Important Difference

- An exploratory analysis of sensitivity to change was conducted using distributional methods to evaluate effect size (mean change score divided by standard deviation of baseline score). Higher values indicated a greater sensitivity to change.
- Preliminary interpretability was assessed with the Minimally Important Difference (MID) defined by the smallest change in a score for a patient that indicated an actual change, which was derived using anchor-based methods (Patient and Clinician Global Impression of Severity).

Results

- The analytic data set was 243 subjects (145 children and 98 parents/guardians); children's average age was 9.2 years, 72% male, and average age at diagnosis was 6.9 years. Parent's average age was 41.6 years, predominantly mothers (80.7%), married (88.1%), and worked full-time (51.0%).
- Factor analyses identified 3 domains: Physical Functioning, Social Well-being, and Emotional Well-being (**Figure 2**).
- Item reduction resulted in an 11-item measure (**Figure 3**).
- Ceiling effects above 66% for items with responses of "Not at all/Never/None" (where respondents could not get any better) were seen in 3 items.
- Internal consistency reliability was acceptable for all domains and Overall score (Cronbach's alpha >0.70).
- At least one of the convergent validity hypotheses for each domain and Overall was proven (r>0.30).
- For known groups validity, Emotional Well-being and Social Well-being scores were able to significantly discriminate between levels of coping. There were trends that younger children had greater disease impact, and children who experienced a larger increase in growth (at 12 weeks) reported higher (better) scores in Physical Functioning scores.
- Associated effect sizes ranged from –0.40 to –0.58, indicating that the GHD-CIM is sensitive to change.
- After reviewing the concordance between child PRO and parent ObsRO versions, it was decided, due to inconsistencies in the validation data between them, to only have an ObsRO version.
  - It is recommended to have an ObsRO version used for parents of children aged 4 to less than 13 years.

Figure 2 ♦ Conceptual Model GHD-CIM



GHD-CIM, Growth Hormone Deficiency – Child Impact Measure

Figure 3 ♦ Final GHD-CIM

The following questions are about the impact of **growth hormone deficiency (GHD)** on your child's functioning and wellbeing. When answering the questions, please check the response box that most closely represents what **you have SEEN or BEEN TOLD by your child or by others about your child**.

If you have not seen or been told anything which informs you how to answer a question, please check the 'Don't Know' response box. Please do not answer any questions based on what you think, base your response only on what you have seen or been told.

If your child has other health conditions, please think only about their GHD when answering these questions. Please check only one response box for each question. There are no right or wrong answers to these questions.

In the past week:	Not at all	A little	Some	Very	Extremely	Don't know
1. How physically strong was your child when doing sports or other physical activities	☐	☐	☐	☐	☐	☐
2. How tired was your child during the day	☐	☐	☐	☐	☐	☐
3. How active was your child	☐	☐	☐	☐	☐	☐

In the past week:	None	A little	Some	A lot	An extreme amount	Don't know
4. How much energy did your child have	☐	☐	☐	☐	☐	☐

In the past week, because of their size, how often:	Never	Rarely	Sometimes	Often	All of the time	Don't know
5. Did people think your child was younger than they are	☐	☐	☐	☐	☐	☐
6. Were they teased.....	☐	☐	☐	☐	☐	☐
7. Were they treated differently by children	☐	☐	☐	☐	☐	☐

The next questions are about your **child's emotions**. Please answer the items based on the **behaviors or emotional reactions you have SEEN or BEEN TOLD by your child or by others about your child**. If you have not seen or been told anything which informs you how to answer a question, please check the 'Don't Know' response box. Please do not answer any questions based on what you think, base your response only on what you have seen or been told.

In the past week, because of their size, how often did your child feel:	Never	Rarely	Sometimes	Often	All of the time	Don't know
8. Embarrassed	☐	☐	☐	☐	☐	☐
9. Nervous or anxious	☐	☐	☐	☐	☐	☐
10. Worried about growing.....	☐	☐	☐	☐	☐	☐
11. Upset.....	☐	☐	☐	☐	☐	☐

GHD-CIM, Growth Hormone Deficiency – Child Impact Measure

Conclusions

- PRO development is an iterative process and measures are refined by the results.
- This validation study resulted in the GHD-CIM ObsRO version for parents/guardians of children aged 4 to less than 13 years.
- The GHD-CIM ObsRO version was found to be reliable and valid and is considered ready for inclusion in clinical trials and clinical practice.
- Accurate and reliable assessment of disease burden can help researchers and clinicians better assess and address impacts of disease, factors that may affect treatment compliance and improve doctor–patient communications.

References

1. Guidance for industry: patient-reported outcomes measures, use in medical product development to support labeling claims (2009). Rockville, MD: U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research: Center for Biologics Evaluation and Research: Center for Devices and Radiological Health; 2. European Medicines Agency. Committee for Medicinal Products for Human use (CHMP). Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. 27 July 2005, London. Available at: https://www.ema.europa.eu/en/regulatory-guidance-use-health-related-quality-life-hrql-measures.

Conflict of interest disclosure

M. Brod and S. Alolga are paid consultants to the pharmaceutical industry, including Novo Nordisk. M.H. Rasmussen, K. Vad, and J. Bedoin are employees of Novo Nordisk, A/S.

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Growth and syndromes (to include Turner syndrome)

Meryl Brod

Poster presented at: ESPE 2019 VIENNA

PosterSessionOnline.com